Different prognostic value of functional right ventricular parameters in arrhythmogenic right ventricular cardiomyopathy/dysplasia

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Abstract: BACKGROUND The value of standard 2-dimensional transthoracic echocardiographic parameters for risk stratification in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is controversial. METHODS AND RESULTS We investigated the impact of RV fractional area change (FAC) and tricuspid annulus plane systolic excursion (TAPSE) for the prediction of major adverse cardiovascular events (MACE) defined as the occurrence of cardiac death, heart transplantation, survived sudden cardiac death, ventricular fibrillation, sustained ventricular tachycardia, or arrhythmogenic syncope. Among 70 patients who fulfilled the 2010 ARVC/D Revised Task Force Criteria and underwent baseline transthoracic echocardiography, 37 (53%) patients experienced MACE during a median follow-up period of 5.3 (interquartile range, 1.8-9.8) years. Average values for FAC, TAPSE, and TAPSE indexed to body surface area (BSA) decreased over time (P=0.03 for FAC, P=0.03 for TAPSE, and P=0.01 for TAPSE/BSA, each versus baseline). In contrast, median RV end-diastolic area increased (P=0.001 versus baseline). Based on the results of Kaplan-Meier estimates, the time between baseline transthoracic echocardiography and experiencing MACE was significantly shorter for patients with FAC <23% (P<0.001), TAPSE <17 mm (P=0.02), or right atrial short axis/BSA 25 mm/m(2) (P=0.04) at baseline. A reduced FAC constituted the strongest predictor of MACE (hazard ratio, 1.08 per 1% decrease; 95% confidence interval, 1.04-1.12; P<0.001) on bivariable analysis. CONCLUSIONS This long-term observational study indicates that TAPSE and dilation of right-sided cardiac chambers are associated with an increased risk for MACE in patients with ARVC/D with advanced disease and a high risk for adverse events. However, FAC is the strongest echocardiographic predictor of adverse outcome in these patients. Our data advocate a role for transthoracic echocardiography in risk stratification in patients with ARVC/D, although our results may not be generalizable to lower-risk ARVC/D cohorts.

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Background—The value of standard 2-dimensional transthoracic echocardiographic parameters for risk stratification in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is controversial.

Methods and Results—We investigated the impact of RV fractional area change (FAC) and tricuspid annulus plane systolic excursion (TAPSE) for the prediction of major adverse cardiovascular events (MACE) defined as the occurrence of cardiac death, heart transplantation, survived sudden cardiac death, ventricular fibrillation, sustained ventricular tachycardia, or arrhythmogenic syncope. Among 70 patients who fulfilled the 2010 ARVC/D Revised Task Force Criteria and underwent baseline transthoracic echocardiography, 37 (53%) patients experienced MACE during a median follow-up period of 5.3 (interquartile range, 1.8–9.8) years. Average values for FAC, TAPSE, and TAPSE indexed to body surface area (BSA) decreased over time (P=0.03 for FAC, P=0.03 for TAPSE, and P=0.01 for TAPSE/BSA, each versus baseline). In contrast, median RV end-diastolic area increased (P=0.001 versus baseline). Based on the results of Kaplan–Meier estimates, the time between baseline transthoracic echocardiography and experiencing MACE was significantly shorter for patients with FAC <23% (P<0.001), TAPSE <17 mm (P=0.02), or right atrial short axis/BSA ≥25 mm/m^2 (P=0.04) at baseline. A reduced FAC constituted the strongest predictor of MACE (hazard ratio, 1.08 per 1% decrease; 95% confidence interval, 1.04–1.12; P<0.001) on bivariable analysis.

Conclusions—This long-term observational study indicates that TAPSE and dilation of right-sided cardiac chambers are associated with an increased risk for MACE in patients with ARVC/D with advanced disease and a high risk for adverse events. However, FAC is the strongest echocardiographic predictor of adverse outcome in these patients. Our data advocate a role for transthoracic echocardiography in risk stratification in patients with ARVC/D, although our results may not be generalizable to lower-risk ARVC/D cohorts. **(*Circ Cardiovasc Imaging*. 2014;7:230-239.)**

Key Words: arrhythmogenic right ventricular dysplasia ■ cardiomyopathies ■ echocardiography

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is an inherited disease characterized by a progressive fibrofatty replacement mainly involving the RV myocardium. It is associated with ventricular arrhythmias, heart failure, and sudden cardiac death (SCD).[1–6]

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RV dilation, reduced RV systolic function, and diffuse RV involvement have previously been studied as predictors of an adverse outcome in patients with ARVC/D but have yielded conflicting results possibly because of divergent imaging modalities, varying parameters measured, and heterogeneous patient cohorts.[7–15] Data about the predictive role of RV fractional area change (FAC) in ARVC/D as measured by 2-dimensional transthoracic echocardiography (2D TTE) are scarce and controversial.[9,14–20]

Tricuspid annulus plane systolic excursion (TAPSE) can easily be determined by M-mode TTE. It is a robust parameter for

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echocardiographic assessment of RV longitudinal systolic function if properly acquired and closely correlates with RV ejection fraction (RVEF); however, it has not been studied as a prognostic measure in ARVC/D so far.[18,21–23] Therefore, the purpose of this longitudinal study was to (1) describe the change of FAC and TAPSE among other conventional echocardiographic parameters during long-term follow-up, and (2) define their prognostic value in a relatively large cohort of patients with ARVC/D.

Methods

Patient Population

The Zurich ARVC Program (www.arvc.ch) was established in 2011 to provide expert clinical care for patients with ARVC/D. Patients were recruited at 3 collaborative Swiss centers (University Hospital Zurich, University Hospital Bern, and Triemli Hospital Zurich). So far, the Zurich ARVC Program has recruited 131 patients ≥15 years of age with a possible, borderline, or definite diagnosis of ARVC/D according to the 2010 Revised Task Force Criteria (TFC).[24] For this study, only patients with a definite or borderline diagnosis, echocardiographic assessment at baseline including measurements of both FAC and TAPSE, and a follow-up duration of ≥3 months were included. Furthermore, patients in whom diagnosis was made by the inclusion of FAC were excluded from the current analysis to avoid interaction bias with disease probability within the Cox proportional hazard model. Thus, within this study, we report data from 70 patients that fulfilled the inclusion criteria (Figure 1). TTE at baseline was defined as the first TTE in which measurements of both FAC and TAPSE were available. There was no patient in whom diagnosis of ARVC/D was based on a reduced RVEF as detected by cardiac magnetic resonance (CMR) tomography. Echocardiography was prospectively analyzed in 28 (40%) and retrospectively analyzed in 42 (60%) patients. Echocardiographic data were interpreted by 2 different observers blinded to the outcome data and to each other. Clinical information regarding demographics and symptoms was obtained from hospital records at the time of baseline TTE. This study was approved by the institutional review board of each participating center, and in accordance with Swiss law, patients gave written informed consent for prospective inclusion into this study.

Echocardiography

From left parasternal, apical, and subcostal windows, conventional M-mode, 2D, and color Doppler echocardiography was performed by an experienced investigator trained in the analysis of the complex anatomy of the right ventricle in all patients using ultrasound transducers with a frequency range between 1 and 5 MHz (Acuson Sequoia C 512; Acuson Corporation, Siemens, Mountain View, CA; Vivid 7 or Vivid E9; GE Vingmed Ultrasound AS, Horten, Norway; iE33; Philips Healthcare, Best, the Netherlands) and according to a standard clinical protocol that did not differ among the 3 centers. Dimensions and function of both ventricles were assessed according to established guidelines for 2D TTE.[25] For FAC, final values were obtained after averaging 2 measurements over 1 cardiac cycle, whereas for all other parameters, 1 measurement was taken. The degree of tricuspid regurgitation was determined as none, mild, moderate, or severe.[26]

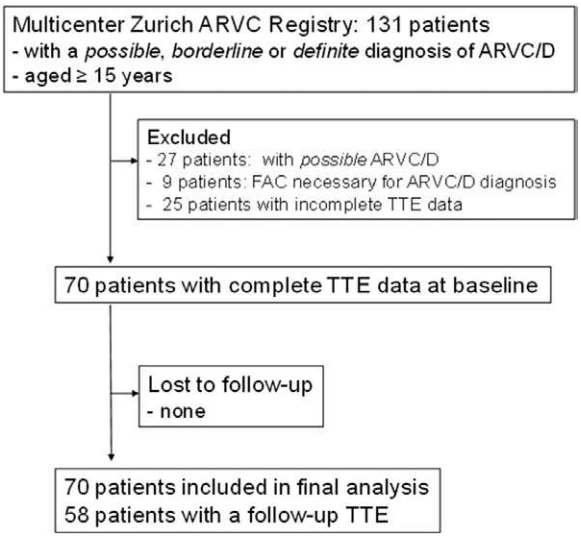

Figure 1. Flow chart. ARVC/D indicates arrhythmogenic right ventricular cardiomyopathy/dysplasia; FAC, fractional area change; and TTE, transthoracic echocardiography.

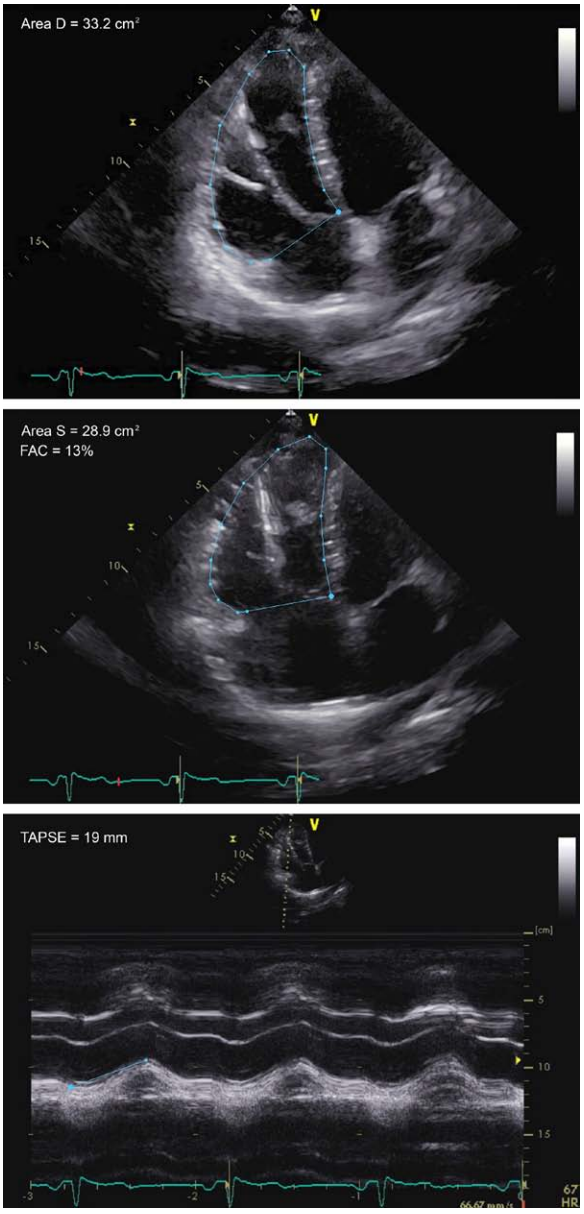

Figure 2. Representative echocardiographic end-diastolic (area D; **top**) and end-systolic (area S; **middle**) right ventricular area measurements (blue lines) taken from the apical 4-chamber view in a patient with definite arrhythmogenic right ventricular cardiomyopathy/dysplasia. M-mode of the lateral tricuspid annular systolic excursion for the measurement of tricuspid annulus plane systolic excursion (tricuspid annulus plane systolic excursion, TAPSE; **bottom**) in this same patient (blue line). FAC indicates fractional area change.

RV Measurements

Echocardiography-derived 2D RV area measurements were taken from the apical 4-chamber view (4CV) at end-diastole (area D) and end-systole (area S), and FAC was defined as the ratio between the difference of the end-diastolic and end-systolic RV areas and the end-diastolic area (FAC=[area D−area S]/area D) as previously reported (Figure 2).[9,23] TAPSE was determined by placing the M-mode cursor perpendicularly through the lateral tricuspid annulus in the 4CV and measuring the amount of longitudinal motion at peak systole (Figure 2).[17,23] A FAC ≥33%[14,24] and a TAPSE ≥17 mm[27] were considered normal. Echocardiographic exams and reports were also reviewed for regional wall motion abnormalities and left ventricular (LV) involvement. LV involvement was considered when regional wall motion abnormalities or a reduced EF (<50% by Simpson biplane method) were present and other causes were excluded.[9,14]

Reproducibility

To determine intra- and interobserver variability, measurements were reanalyzed by the same observer (at least 1 week after the first measurement) and by an independent observer in 31 randomly selected cases.

Follow-Up and Definitions

Follow-up for survival data was performed by review of hospital charts, including implantable cardioverter defibrillator (ICD) interrogations with stored electrograms, Holter ECGs, clinical visits, and telephonic interviews of patients, their relatives, or treating physicians. The role of FAC, TAPSE, and other parameters on long-term clinical outcome was compared in 2 patient groups: (1) patients with major adverse cardiovascular events (MACE)—adverse outcome (composite of cardiac death, heart transplantation, survived SCD, ventricular fibrillation [VF], sustained ventricular tachycardia [VT], and arrhythmogenic syncope), and (2) all remaining patients—favorable outcome. For Kaplan–Meier estimates and Cox regression analyses, time from baseline to MACE was the event of interest. Survived SCD, VF, sustained VT, and arrhythmogenic syncope were defined as previously reported.[28]

Statistical Analysis

Continuous variables are presented as mean±SD or median (interquartile range [ICR]). Categorical variables are reported as frequency (percentage). Comparisons between groups with a favorable outcome and MACE (Tables 1 and 2) were performed by the 2-sided unpaired Student *t*-test (normal distribution) or the Mann–Whitney *U*-test (skewed distribution) for continuous variables, and by Fisher exact

Table 1. Baseline Clinical Characteristics

Patient Characteristics	All Patients (n=70)	Outcome		*P* Value
		Favorable (n=33)	MACE (n=37)	
Men, n (%)	47 (67%)	26 (79%)	21 (57%)	0.07
Age, y, mean±SD	42.9±14.7	45.5±13.9	40.6±15.2	0.17
Systolic blood pressure, mm Hg, mean±SD	121±19	126±21	116±15	0.02
Diastolic blood pressure, mm Hg, mean±SD	75±11	77±13	73±10	0.09
Heart rate, beats/min, median (IQR)	63 (55–72)	62 (55–71)	64 (55–73)	0.96
Body surface area, m^2, 1. TTE, mean±SD	1.89±0.21	1.9±0.2	1.86±0.2	0.07
Definite ARVC/D, n (%)	53 (76%)	21 (64%)	32 (86%)	0.05
Borderline ARVC/D, n (%)	17 (24%)	12 (36%)	5 (14%)	0.05
Previous syncope, n (%)	20 (29%)	6 (18%)	14 (38%)	0.11
Previous aborted SCD, n (%)	2 (3%)	1 (3%)	1 (3%)	1.00
Previous sustained VT/VF, n (%)	40 (57%)	14 (42%)	26 (70%)	0.03
CMR data available, n (%)	18 (26%)	10 (30%)	8 (22%)	0.43
RV ejection fraction <40%, n (%)	8 (44%)	3 (30%)	5 (63%)	0.34
Major criterion according to 2010 TFC, n (%)	13 (72%)	6 (60%)	7 (88%)	0.31
Minor criterion according to 2010 TFC, n (%)	2 (11%)	1 (10%)	1 (13%)	1.00
Family history of SCD <35 y, n (%)	4 (6%)	2 (6%)	2 (5%)	1.00
Endomyocardial biopsy, n (%)	5 (7%)	2 (6%)	3 (8%)	1.00
Major criterion according to 2010 TFC, n (%)	1 (20%)	0	1 (33%)	1.00
Minor criterion according to 2010 TFC, n (%)	1 (20%)	1 (50%)	0	1.00
Medication				
Amiodarone, n (%)	14 (20%)	5 (15%)	9 (24%)	0.15
β-Blocker, n (%)	38 (54%)	13 (39%)	25 (68%)	< 0.001
Sotalol, n (%)	13 (19%)	5 (15%)	8 (22%)	0.24
ACE-I/ARB, n (%)	23 (33%)	11 (33%)	12 (32%)	0.46

P values were calculated by 2-sided unpaired Student *t*-test (normal distribution) or Mann–Whitney *U*-test (skewed distribution) for continuous variables, and by Fisher exact test for categorical variables. Values are means±standard deviation, medians with interquartile ranges and numbers (percentages). 1. TTE indicates baseline transthoracic echocardiography; ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ARVC/D, arrhythmogenic right ventricular cardiomyopathy/dysplasia; CMR, cardiac magnetic resonance; IQR, interquartile range; MACE, major adverse cardiovascular events; SCD, sudden cardiac death; TFC, Revised Task Force Criteria; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Table 2. Baseline Echocardiographic Variables in Patients With a Favorable and Those With an Adverse Outcome (MACE)

Variables	Favorable Outcome (n=33)	MACE (n=37)	*P* Value
FAC <33%, n (%)	12 (36%)	29 (78%)	<0.001
FAC <23%, n (%)	4 (12%)	17 (46%)	0.004
FAC, %, mean±SD	35±10	25±9	<0.001
TAPSE <17 mm, n (%)	5 (15%)	15 (41%)	0.03
TAPSE, mm, mean±SD	21±5	18±5	0.02
TAPSE/BSA, mm/m^2, mean±SD	11.1±2.8	9.9±2.7	0.07
RVEDA ≥28 cm^2, n (%)	9 (27%)	18 (49%)	0.09
RVEDA, cm^2, median (IQR)	24.1 (21.5–28)	28 (25.3–35.6)	0.1
RVEDA/BSA, cm^2/m^2, median (IQR)	12 (11–15.4)	14.8 (13–19)	0.22
RA short axis/BSA ≥25 mm/m^2, n (%)	4 (12)	14 (38)	0.03
RA short-axis diameter/BSA, mm/m^2, median (IQR)	20.4 (18.2–22.7)	22.5 (19.7–26.8)	0.17
RA short-axis diameter, mm, median (IQR)	39.5 (35.9–43.7)	43 (38–53.3)	0.28
RA long-axis diameter, mm, median (IQR)	50 (47–53.7)	52.5 (47.2–58)	0.36
RWA in <2 regions, n (%)	14 (42%)	16 (43%)	1.00
Patients with RWA, n (%)	28 (85%)	28 (76%)	0.38
Moderate/severe tricuspid regurgitation, n (%)	1 (3%)	7 (19%)	0.06
LV ejection fraction, %, mean±SD	57±7	55±13	0.39
LA diameter/BSA ≥23 mm/m^2, n (%)	2 (61%)	9 (24%)	0.09
LA diameter/BSA, mm/m^2, mean±SD	19.4±3.1	20.2±4.1	0.35

P values were calculated by 2-sided unpaired Student *t*-test (normal distribution) or Mann–Whitney *U*-test (skewed distribution) for continuous variables, and by Fisher exact test for categorical variables. BSA indicates body surface area; FAC, fractional area change; IQR, interquartile range; LA, left atrial; RA, right atrial; RVEDA, right ventricular end-diastolic area; RWA, regional wall motion abnormalities defined as akinesia or dyskinesia; and TAPSE, tricuspid annular plane systolic excursion.

test for categorical variables. For comparison of echocardiographic data between baseline and follow-up, we used the paired Student *t*-test (normal distribution) or the Wilcoxon signed-rank test (skewed distribution) for continuous variables and the McNemar test (without continuity correction) for categorical variables. Spearman correlation was performed to analyze correlations between TTE and CMR parameters. Cumulative probabilities of survival free of MACE were determined by the Kaplan–Meier method. We applied the Grambsch and Therneau method for testing the proportional hazards assumption for univariable Cox models. There was no evidence that proportionality assumption was not fulfilled. Accordingly, baseline variables that were significantly associated with MACE were identified by univariable Cox regression analysis, and differences in survival between groups were calculated with the log-rank test. The performance of TAPSE and FAC for classifying an end point was measured using Harrell *c*-statistic, which accounts for censored measurements. Additionally, we calculated receiver operating characteristic curves and derived sensitivity and specificity for the determined cut-off values. The cut-off values for FAC and TAPSE were determined as follows: the log-rank test of all cut-off points between the 20th and 80th percentiles was calculated, and the cut-off with the minimal adjusted *P* value was chosen according to the formula by Altman.[29] For the purpose of this study, we were mainly interested in echocardiographic variables at initial assessment that could be important to predict MACE in patients with ARVC/D. Based on the univariable Cox regression analysis, we performed separate bivariable analyses with the only 2 RV functional echocardiographic parameters (FAC and TAPSE) and with the 2 right-sided dimensional echocardiographic parameters that yielded the lowest *P* values in univariable analysis (RV end-diastolic area [RVEDA] and right atrial [RA] short-axis diameter). These bivariable analyses were performed to better delineate the prognostic properties of each RV functional and right-sided dimensional parameter on adverse outcome. The initial echocardiographic assessment will guide the physician to choose an appropriate therapy for each individual patient based on the risk for MACE. As in most clinical cases, it is not appropriate to wait for an assessment of changes of functional and structural echocardiographic parameters to evaluate the patient's risk for MACE; we have not used time-updated echocardiographic parameters to predict MACE. Intraclass correlation (ICC) was used to quantify intra- and interobserver variability, with ICC values >0.75 representing good reliability of measurements. A 2-sided *P* value <0.05 was considered significant. Statistical analysis was performed using R programming language (R Development Core Team 2009) and GraphPad Prism 5 (GraphPad Software Inc, La Jolla, CA).

Results

Patient Population

Of 131 patients screened in the 3 centers, 70 had a complete echocardiographic examination at baseline and were included in the study (Figure 1). All of these were referred as index patients with a definite or borderline diagnosis of ARVC/D according to the 2010 TFC. Borderline cases fulfilled 1 major and 1 minor (n=13) or 3 minor (n=4) criteria. Baseline characteristics are provided in Table 1.

Echocardiographic Characteristics at Baseline

Echocardiographic data are presented in Tables 2 and 3. Ten (14%) patients had echocardiographic evidence of LV involvement at baseline. When the reference values were indexed to BSA, 15 (21%) patients had a reduced TAPSE <7 mm/m^2, 44 (63%) patients a dilated RV >12.3 cm^2/m^2, 18 (26%) patients a dilated RA (short axis >25 and long axis >30 mm/m^2), and 10 (14%) patients a dilated LA >23 mm/m^2.[30] FAC correlated better with RVEF as determined by CMR than TAPSE (r=0.480; P=0.05 for FAC versus RVEF; r=0.34; P=0.19 for TAPSE versus RVEF).

Echocardiographic Changes During Long-Term Follow-Up

From the whole cohort, a follow-up TTE was available in 58 patients. Of those, 33 patients belonged to the MACE group and 25 patients to the favorable group (P=0.21). The median time between baseline TTE and follow-up TTE was 2244 (IQR, 1099–3591; range, 95–9744) days. More patients had LV involvement compared with baseline (29% versus 14%; P=0.02). Averaged for all patients in whom a follow-up measurement was available, median FAC, mean TAPSE, and mean TAPSE indexed to BSA decreased over time (P=0.03 for FAC; P=0.03 for TAPSE; P=0.01 for TAPSE/BSA, each versus baseline). In contrast, median RVEDA increased (P=0.001 versus baseline). TAPSE decreased in 47% of patients,

Table 3. Echocardiographic Variables at Baseline and Follow-Up

Variables	First TTE (n=70)	Follow-Up TTE (n=58)	*P* Value
Patients with RWA, n (%)	56 (80%)	52 (90%)	0.01
RWA of subtricuspid region, n (%)	47 (67%)	50 (86%)	<0.001
RWA in ≥2 regions, n (%)	40 (57%)	42 (72%)	0.16
TAPSE, mm, mean±SD	19.7±5.4	18.8±5.4	0.03
TAPSE <17 mm, n (%)	20 (29%)	20 (34%)	0.48
TAPSE/BSA, mm/m^2, mean±SD	10.5±2.8	9.9±2.9	0.01
RV FAC, %, median (IQR)	30 (20–38.3)	26.5 (20.3–34)	0.03
RV FAC <33%, n (%)	41 (59%)	38 (66%)	0.64
LV ejection fraction, %, median (IQR)	57.5 (51–64)	55 (47.78–63)	0.04
RVEDA, cm^2, median (IQR)	26.1 (22.5–29.6)	29.8 (24.7–35)	0.001
RVEDA/BSA, cm^2/m^2, median (IQR)	13.6 (11.7–17.1)	15.6 (13.2–18.8)	0.003
LA diameter/BSA, mm/m^2, median (IQR)	20 (17.3–21.6)	19.4 (17.9–21.7)	0.86
RA short-axis diameter, mm, median (IQR)	42 (36–47)	42 (36–53)	0.29
RA short-axis diameter/BSA, mm/m^2, median (IQR)	21.4 (19.3–25.3)	22.2 (19.1–27.7)	0.54
RA long-axis diameter, mm, median (IQR)	51 (47–56)	53 (48–57)	0.5
RA long-axis diameter/BSA, mm/m^2, median (IQR)	27 (23.9–30.1)	27.4 (23.2–31.1)	0.9
Moderate/severe tricuspid regurgitation, n (%)	8 (14%)	6 (10%)	0.16

P values were calculated by 2-sided paired Student *t*-test (normal distribution) or Wilcoxon signed-rank test (skewed distribution) for continuous variables and by McNemar test for categorical variables. BSA indicates body surface area; FAC, fractional area change; IQR, interquartile range; LA, left atrial; RA, right atrial; RVEDA, right ventricular end-diastolic area; RWA, regional wall motion abnormalities defined as akinesia or dyskinesia; TAPSE, tricuspid annular plane systolic excursion; and TTE, transthoracic echocardiography.

whereas there was no change in 24% and an increase in 29% (range of change, −10 to +8 mm). TAPSE adjusted for BSA decreased in 45% of patients, whereas there was no change in 29% and an increase in 26% (range of change, −5 to +4 mm/m^2). FAC decreased in 57% of patients, whereas there was no change in 4% and an increase in 39% (range of change, −33% to +18%). RVEDA increased in 63% of patients, no change in 11%, and a decrease in 26% (range of change, −15 to +25 cm^2). Figure 3 depicts the data for FAC and TAPSE at baseline and their changes during long-term follow-up in patients from whom measurements of both parameters were available. A significant positive correlation between baseline FAC and TAPSE (r=0.5; P<0.001) and a negative correlation between baseline FAC and baseline right chamber dimensions (r=–0.57; P<0.001 for FAC versus RVEDA; r=–0.44; P<0.001 for FAC versus RA short axis/BSA) were observed. There was no evidence for an association between an impaired TAPSE and subtricuspidal regional wall motion abnormalities (P=1.0).

Predictors of Clinical Outcome

Over a median follow-up period of 5.3 (IQR 1.8–9.8) years, 37 (53%) patients experienced MACE (Table 4). Median follow-up was not significantly different between patients with favorable versus those with an adverse outcome (4.4 years; IQR 1.6–8.1 versus 6.3 years; IQR 2.1–10.5 years, respectively; P=0.48). No patient died. Heart transplantation was performed in 5 patients (due to incessant VT/VF combined with heart failure in 3 patients and heart failure only in 2 patients). The most frequent MACE were survived sustained VT (67%) and VF (19%). Thirty-one (63%) of 49 patients with an ICD experienced an appropriate ICD intervention. This intervention was because of VT in 24 patients and VF in 7 patients. Table 2 shows baseline echocardiographic parameters in patients with favorable outcome and those with MACE. Variables analyzed as potential predictors of MACE are presented in Table 5. A lower FAC and TAPSE as well as an increased RVEDA and RA short-axis diameter were identified as univariable predictors (Table 5). In bivariable analyses stratified into functional and dimensional echocardiographic parameters, FAC (functional parameter), RVEDA, and RA short-axis diameter (dimensional parameters) remained independent predictors of MACE. A reduced FAC constituted the strongest predictor of MACE (hazard ratio, 1.08 per 1% decrease; 95% confidence interval [CI], 1.04–1.12; P<0.001) on bivariable analysis. Consistent with this observation, Harrell *c*-statistic for FAC equaled 0.67 and for TAPSE 0.61, demonstrating that the measurement of baseline FAC had a better predictive value compared with baseline TAPSE. Figure 4 illustrates the results of the receiver operating characteristic analysis for distinguishing patients with MACE from those without. For baseline FAC, a sensitivity >80% for predicting MACE was obtained at a cut-off <23% (sensitivity, 88%; 95% CI, 73–95%) and for baseline TAPSE at a cut-off <17 mm (sensitivity, 85%; 95% CI, 69–93%), yet both parameters displayed a limited specificity for these cut-off values (FAC, 46%; 95% CI, 31–62%; TAPSE, 41%; 95% CI, 26–57%). Patients with a FAC <23% or a TAPSE <17 mm had a cumulative probability for MACE ≈75% after 2 years (Figure 5), which was higher than for patients with a FAC ≥23% (P log-rank unadjusted and adjusted <0.001) and a TAPSE ≥17 mm (P log-rank unadjusted=0.02, adjusted=0.19).

Reproducibility

For interobserver variability, ICC values were 0.50 (95% CI, 0.18–0.72) for FAC and 0.83 (95% CI, 0.67–0.91) for TAPSE, whereas for intraobserver variability, ICC values were 0.59 (95% CI, 0.30–0.86) for FAC and 0.86 (95% CI, 0.72–0.93) for TAPSE.

Discussion

In this longitudinal study, we analyzed a relatively large cohort of patients with ARVC/D from 3 tertiary care centers regarding their long-term clinical outcome based on echocardiographic findings at initial presentation. Our study provides evidence that echocardiographic parameters can be applied to predict the clinical outcome in ARVC/D. The main findings are as follows: (1) FAC at baseline is the strongest echocardiographic predictor of MACE; (2) reduced TAPSE and increased

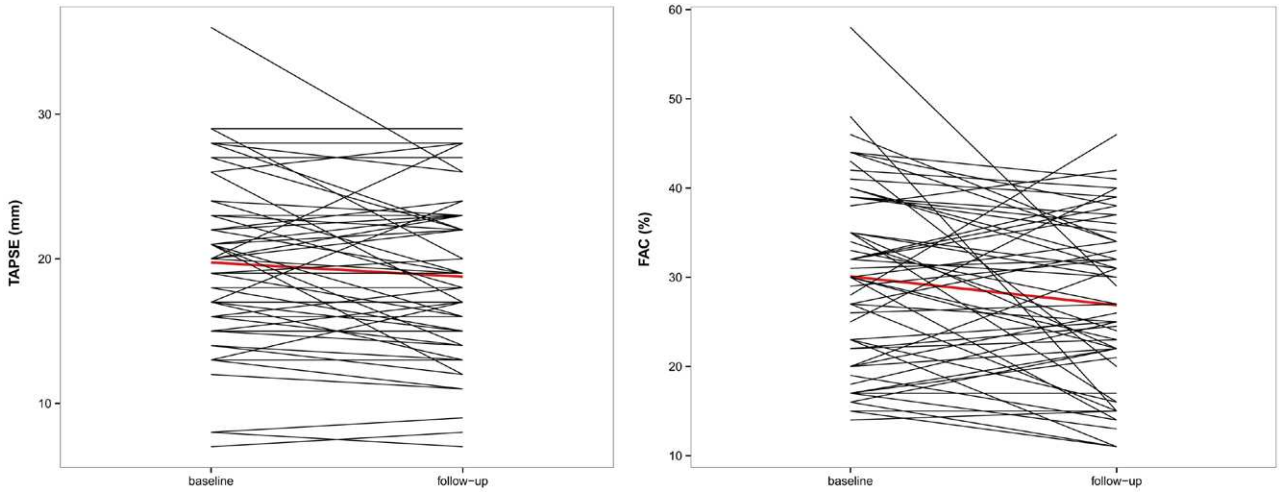

Figure 3. Individual data (black lines) and average values (red line) for tricuspid annulus plane systolic excursion (TAPSE; **left**) and right ventricular fractional area change (FAC; **right**) at baseline and their change during long-term follow-up from patients in whom a follow-up transthoracic echocardiography (n=58) was available. *P* values were calculated by 2-sided paired Student *t*-test (normal distribution) or Wilcoxon signed-rank test (skewed distribution).

right-sided chamber dimensions at baseline are associated with an increased risk of MACE; (3) TAPSE is associated with lower intra- and interobserver variability compared with FAC; and (4) on average, both FAC and TAPSE decrease during long-term follow-up, whereas right-sided chamber dimensions increase.

Natural History

Previous echocardiographic studies have demonstrated that RV dilation and reduced regional or global RV function are important features of ARVC/D.[31–33] Our study underscores that ARVC/D is a progressive disease.[8,31,34] During long-term follow-up, right chamber dimensions significantly increased, whereas both FAC and TAPSE decreased. Moreover, LV involvement increased by 2.3-fold compared with baseline, with almost one third of patients demonstrating biventricular disease at follow-up. In line with previous findings from a smaller ARVC/D cohort from Scandinavia, FAC and TAPSE did not decrease, and RVEDA did not increase in a substantial proportion of patients. This reflects some heterogeneity in the individual disease course but may also be related to variability in the measurement of those echocardiographic parameters.[34] Our results differ from those of a smaller Italian ARVC/D cohort in which RVEF and RV end-diastolic volume as determined by 2D TTE did not change significantly between baseline and long-term follow-up.[35] A likely explanation for this discrepancy may be related to differences in the assessment of RV function and dimension, as well as a lack of power to detect significant differences occurring over time due to small sample size.

Table 4. Specification of Major Adverse Cardiovascular Events (MACE) During Follow-Up

MACE	n=37
Cardiac death	0
Heart transplantation	2 (5%)
Ventricular fibrillation	7 (19%)
Sustained ventricular tachycardia	25 (67%)
Arrhythmic syncope	3 (8%)

Values are numbers (percentages).

Predictive Role of Echocardiographic Variables

Different ARVC/D cohorts independently confirmed that spontaneous ventricular tachyarrhythmias, syncope, heart failure, LV involvement, and inducibility of sustained ventricular arrhythmias constitute the risk factors for MACE.[8,9,12–14,28,36] Yet previous studies have yielded conflicting evidence regarding the usefulness of RV function and dimension for risk prediction in ARVC/D.[7–15,37] Controversial findings by others may be related to different study methodologies, divergent imaging modalities, and heterogeneous patient cohorts. Neither occurrence nor severity of RV disease was defined homogenously throughout these studies. A large international multicenter study, Multidisciplinary Study of Right Ventricular Dysplasia, has defined diffuse RV involvement as severe regional involvement in ≥2 RV regions or an RVEF ≤45%.[12] Yet imaging modalities to measure these parameters have not been standardized across different centers.[19] Data about the predictive role of FAC reflecting RVEF in a single 2D plane acquired in the 4CV are scarce in patients with ARVC/D, and 3 previous studies analyzing the predictive role of FAC in ARVC/D came to different conclusions.[9,14,15] Echocardiographic assessment of RV dimension and function is challenging because of the complex RV geometry, and both FAC and TAPSE do not always correlate well with the more accurate 3-dimensional volumes and EF obtained by CMR.[16–20] This is particularly true for FAC, which depends on an optimal image quality. FAC also does not fully reflect the regional function of the RV outflow tract and subtricuspid area that are often involved in ARVC/D.[14] Furthermore, FAC consistently displayed higher intra- and interobserver variability compared with TAPSE in previous studies as well as the present study, which may also be related to the fact that we did not exclude any patient due to difficulties in measuring FAC. Yet both parameters showed good ICC in our analysis.[23,38] Despite these limitations, the current study demonstrates that even small reductions in FAC were associated with MACE,

Table 5. Baseline Variables Associated With Major Adverse Cardiovascular Events

	Univariable Analysis		Bivariable Analysis		Bivariable Analysis	
Variables	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
FAC <33%	3.12 (1.42–6.87)	0.005				
FAC <23%	4.49 (2.25–8.97)	<0.001				
FAC, %, per unit decrease	1.08 (1.04–1.12)	<0.001	1.08 (1.04–1.12)	<0.001		
TAPSE <17 mm	2.15 (1.10–4.17)	0.02				
TAPSE, mm, per unit decrease	1.05 (0.99–1.12)	0.09	1.01 (0.94–1.08)	0.73		
TAPSE/BSA, mm/m^2, per unit decrease	1.09 (0.98–1.2)	0.12				
RVEDA ≥28 cm^2	2.96 (1.48–5.91)	0.002				
RVEDA, cm^2, per unit increase	1.05 (1.02–1.09)	<0.001			1.05 (1.01–1.08)	0.004
RVEDA/BSA, cm^2/m^2, per unit increase	1.08 (1.03–1.14)	0.002				
RA short axis/BSA ≥25 mm/m^2	2.03 (1.03–3.99)	0.04				
RA short axis/BSA, mm/m^2, per unit increase	1.06 (1.01–1.12)	0.02				
RA short axis, mm, per unit increase	1.04 (1.01–1.07)	0.01			1.03 (1.00–1.06)	0.037
RA long axis, mm, per unit increase	1.03 (1.00–1.06)	0.06				
RWA in <2 regions	0.48 (0.22–1.08)	0.08				
Absence of RWA	0.64 (0.24–1.72)	0.38				
Moderate/severe tricuspid regurgitation	1.99 (0.71–5.55)	0.19				
LV ejection fraction, %, per unit decrease	1.01 (0.98–1.04)	0.54				
LA/BSA ≥23 mm/m^2	1.93 (0.88–4.25)	0.10				
LA/BSA, mm/m^2, per unit increase	1.03 (0.95–1.12)	0.46				
Age per year increase	0.99 (0.97–1.01)	0.43				
Sex (HR for women vs men)	0.77 (0.38–1.56)	0.47				
Definite ARVC/D	1.04 (0.47–2.27)	0.93				

P values were calculated by univariable and bivariable Cox-regression. ARVC/D indicates arrhythmogenic right ventricular cardiomyopathy/dysplasia; BSA, body surface area; CI, confidence interval; FAC, fractional area change; HR, hazard ratio; LA, left atrial; LV, left ventricular; RA, right atrial; RVEDA, right ventricular end-diastolic area; RWA, regional wall motion abnormalities; and TAPSE, tricuspid annular plane systolic excursion.

and that a reduced FAC was the strongest predictor of MACE on univariable and bivariable Cox regression analysis. Of note, an FAC >33%, which is proposed as the lower normal range in the current guidelines,[19] still conferred a 3-fold increased risk for adverse events and supports the 2010 TFC, in which the combination of regional wall motion abnormalities and an FAC between 33% and 40% are considered minor criteria for ARVC/D diagnosis.[12]

Although angle-dependent, TAPSE can easily be determined by M-mode echocardiography, is less dependent on image quality, and constitutes a robust and reproducible parameter for the echocardiographic assessment of RV function in ARVC/D. It also correlates well with RVEF determined by CMR or angiography.[16,20–23,39,40] The low intra- and interobserver variability for TAPSE in the current study is consistent with those previous findings. TAPSE has the potential to discriminate well between patients with ARVC/D and healthy probands.[18,33] Although TAPSE has evolved as an important prognostic parameter in other cardiac pathologies such as pulmonary hypertension, myocarditis, and dilated cardiomyopathy,[16,17,41] it has not been studied as a prognostic marker in ARVC/D. To our knowledge, our study is the first

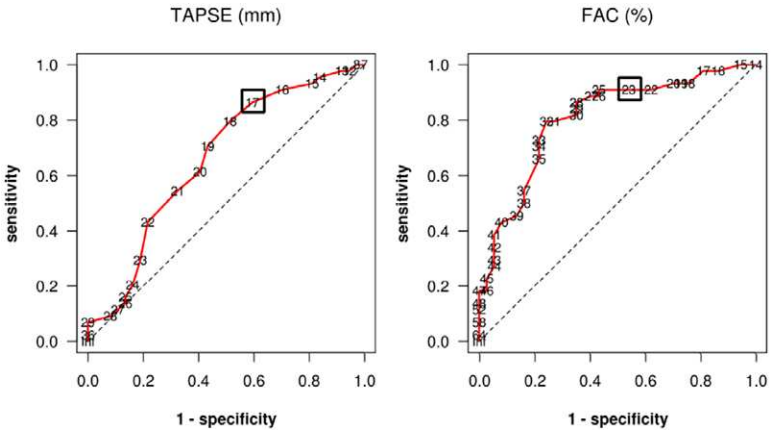

Figure 4. Results of the receiver operating characteristic analysis for tricuspid annulus plane systolic excursion (TAPSE) and fractional area change (FAC; n=70). TAPSE <17 mm and FAC <23% at baseline provided the best sensitivity and specificity for predicting major adverse cardiovascular events in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. Numbers shown in the black box indicate the corresponding cut-off values for TAPSE and FAC, respectively.

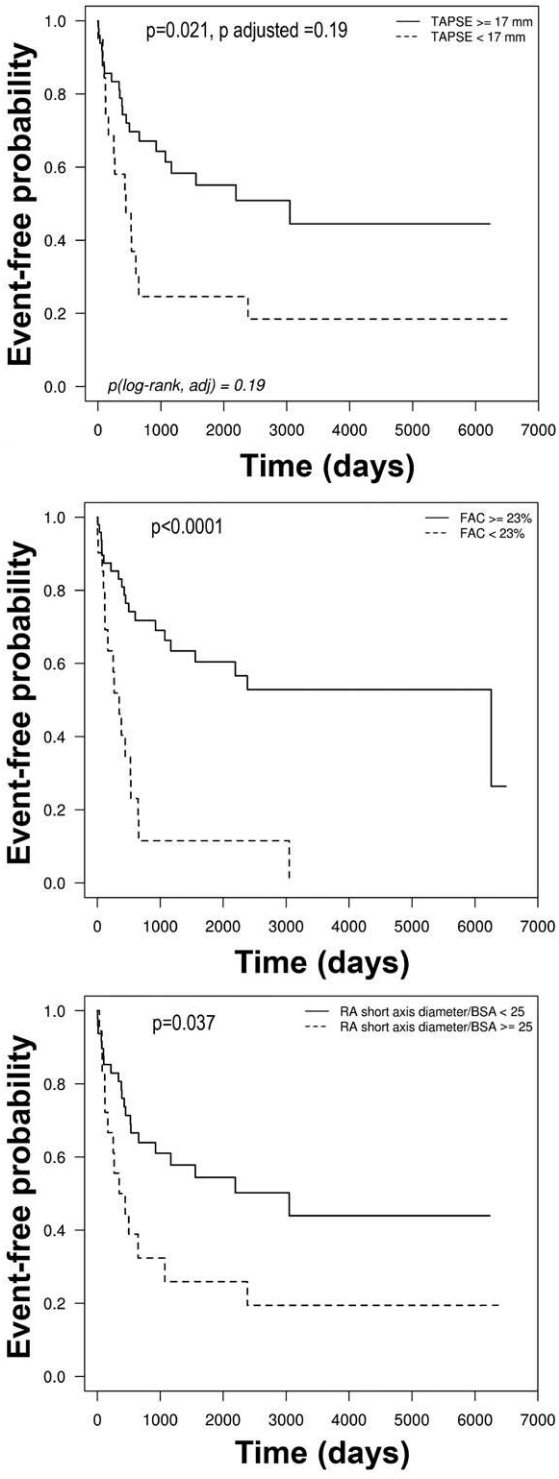

Figure 5. Kaplan–Meier analysis (n=70) of freedom from major adverse cardiovascular events from baseline transthoracic echocardiography stratified by a tricuspid annulus plane systolic excursion <17 mm (**top**; unadjusted *P*=0.02 and adjusted *P*=0.19), a fractional area change (FAC) <23% (**middle**; unadjusted and adjusted *P*<0.001), and a right atrial (RA) short axis/body surface area (BSA) ≥25 mm/m^2 (**bottom**; *P*=0.037; prespecified cut-off value, thus adjustment not necessary).

to demonstrate that TAPSE may be valuable for predicting MACE in ARVC/D. A value of TAPSE <17 mm best identified patients with MACE. However, TAPSE was inferior to FAC with regard to its predictive value and also correlated less well with RVEF as determined by CMR, which may well be related to the fact that TAPSE only represents the longitudinal systolic movement of the RV lateral free wall and hence does not reflect the entire RV systolic function. This property may constitute a particular drawback in patients with ARVC/D, which can affect multiple regions of the RV. Such a regional heterogeneity in systolic function is certainly better reflected by FAC. Another new finding of our study is the predictive value of RA dilation as previously shown in Eisenmenger Syndrome.[30,42] This finding is in line with a recent study showing a prognostic impact of significant tricuspid regurgitation in ARVC/D.[14]

Limitations

This study analyzing patient data from 3 Swiss tertiary care centers may have limitations in patient selection and risk stratification by its observational nature. Of note, we studied a rather high-risk cohort of patients with ARVC/D, given the fact that 57% of our patients had a sustained episode of VT/VF before baseline echocardiography and given the observed high MACE rates. Definite disease was more common in the MACE group at baseline, although definite disease was not associated with MACE in Cox regression analysis. Thus, our data may not be generalizable to other, potentially lower-risk ARVC/D populations. Yet we analyzed whether the patients who were excluded from the final analysis constituted a lower-risk population than those included. In patients with a borderline and definite diagnosis of ARVC/D, MACE were observed in 17 of 34 (50%) excluded patients compared with 37 of 70 (53%) included patients, minimizing the risk of selection bias toward a higher-risk population within our ARVC/D cohort. Although the studied cohort was not small for patients with ARVC/D, the sample size limits the ability to control for all confounders in multivariable analysis. Although median follow-up was not significantly different between patients with a favorable outcome and those with MACE, from a clinical perspective, we cannot fully exclude that the median difference of 1.9 years may have contributed to more adverse events observed in the MACE group and that MACE may also have occurred in the favorable group if follow-up period would have been equal. When RV function is regionally impaired in areas not imaged in the 4CV, such as the RV outflow tract, FAC may be an imperfect measure of RV systolic function. Therefore, FAC may perform less well as a predictor of MACE in those patients. Furthermore, the assessment of RV function with FAC and TAPSE may be limited by the acoustic shadowing of ICD leads. The advent of tissue Doppler imaging and recently strain imaging and 3-dimensional tools may improve both diagnosis and risk stratification in ARVC/D,[15,18,33,43] although their use is still hampered by wide variations, noise artifacts, limited availability, and intervendor variations.[18,43–45]

Conclusions

This long-term observational study indicates that TAPSE and dilation of right-sided cardiac chambers are associated with an increased risk for MACE in patients with ARVC/D with advanced disease and a high risk for adverse events. However, FAC is the strongest echocardiographic predictor of adverse

outcome in these patients. Our data advocate a role for TTE in risk stratification in patients with ARVC/D, although our results may not be generalizable to lower-risk ARVC/D cohorts.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Data on risk stratification in arrhythmogenic right ventricular cardiomyopathy/dysplasia are scarce. Moreover, the natural history of arrhythmogenic right ventricular cardiomyopathy/dysplasia is still being defined. Current guidelines suggest that severe right ventricular (RV) dilation and extensive RV involvement are risk factors for an adverse outcome. However, the different stages of RV dilation and RV involvement are not well defined. Our study helps to understand the clinical course of the disease, as it generally demonstrates an increase in RV area and a decline in RV function during long-term follow-up. We demonstrate that patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia who have a RV fractional area change <23% and a tricuspid annulus plane systolic excursion <17 mm, transthoracic echocardiographic measurements that can noninvasively be obtained by the practicing cardiologist at initial assessment, are at increased risk for an adverse outcome and may benefit from an implantable cardioverter defibrillator. If these novel findings can be confirmed in other populations with arrhythmogenic right ventricular cardiomyopathy/dysplasia, they will provide the necessary evidence for considering prophylactic implantable cardioverter defibrillator insertion in such patients.